## Communications to the Editor

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# SYNTHESIS OF TRIFLUOROMETHYLATED LACTONE AND EPOXIDE

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Trifluoromethylated lactone (6,8) and epoxy esters (15,16) were stereoselectively prepared through the iodolactonization.

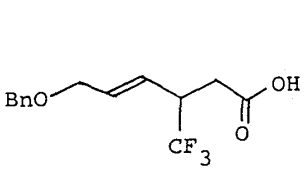
KEYWORDS —— 3-trifluoromethyl-γ-butyrolactone; trifluoromethylated threo- epoxide; trifluoromethylated erythro-epoxide; iodolactonization

The synthetic utility of iodolactonization has been well demonstrated.[1] In our research on the preparation of the trifluoromethylated analogs of biologically active compounds, it was necessary to carry out the stereoselective synthesis of the trifluoromethylated compound. In this communication, we describe the iodolactonization of carboxylic acid (1), amide (2)[2] and the conversion of the iodolactone to hydroxylactone via epoxy acid.

On treatment of 1 with iodine-potassium iodide in aqueous sodium bicarbonate, two compounds were obtained in a 6:1 ratio (71%).[3] They could be easily separated by flash chromatography. The structures of 3 and 4 were determined by a comparison of the coupling constants of the ring protons, Ha and Hb, 3.9 Hz for 3 and 5.1 Hz for 4. On the basis of the concerted anti attack of iodine and the carboxyl group on the E-double bond, an assumption was made as to the configuration of the iodine atom.

An attempt was made to improve the ratio of the thermodynamically favored trans-lactone (3) by the method described by Bartlet,[4] but this could not be done and decomposition occurred. In the case of amide (2), syn-2 gave the lactonized compound (5) under iodine-aq. THF conditions (68%). No reaction occurred for the anti-2 isomer under essentially the same reaction conditions because of the steric repulsion of the two consecutive substituents (cis-relationship) in the transition state (see Figure). Lactone (5) was converted to the β-trifluoromethylbutenolide derivative by heating in toluene. To substitute the iodine atoms of 3 and 4 with a hydroxyl group, 3 and 4 were treated with base (2 N KOH) followed by acid (10% HCl). The trans-isomer (3) gave a cis-product (6) in 87% yield on treatment of the intermediately isolable epoxy acid (7) with trifluoroacetic acid. The cis-isomer (4) gave a trans-product (8) directly in a 79% yield under identical conditions. The structures of 6 and 8 were determined by comparing the coupling constants of the ring protons (Ha, Hb) (5.6 Hz and 3.1 Hz , respectively) and trans-opening of the epoxide.

The structure of 8 was confirmed by a comparison with compound 9 derived stereospecifically from 10 by reducing the double bond with sodium borohydride. The threo-relationship of 10 has already been established by converting 10 to the trifluoromethylated sugar derivative (11) whose structure was determined by X-ray



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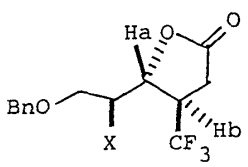
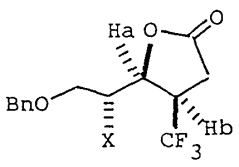


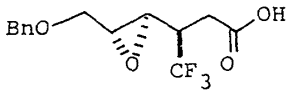
3 X=I , $J_{Ha-Hb}$=3.9Hz



4 X=I , $J_{Ha-Hb}$=5.1Hz

8 X=OH, $J_{Ha-Hb}$=3.1Hz

6 X=OH, $J_{Ha-Hb}$=5.6Hz



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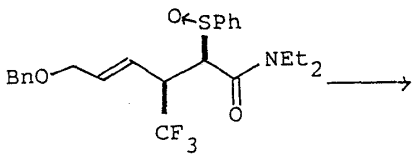
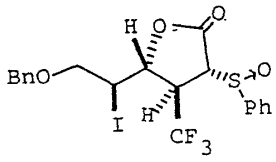


syn-2



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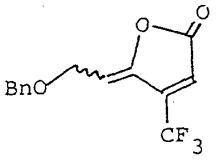
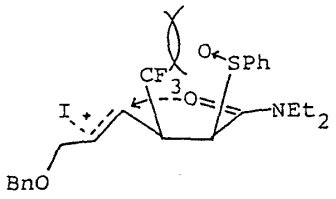


anti-2

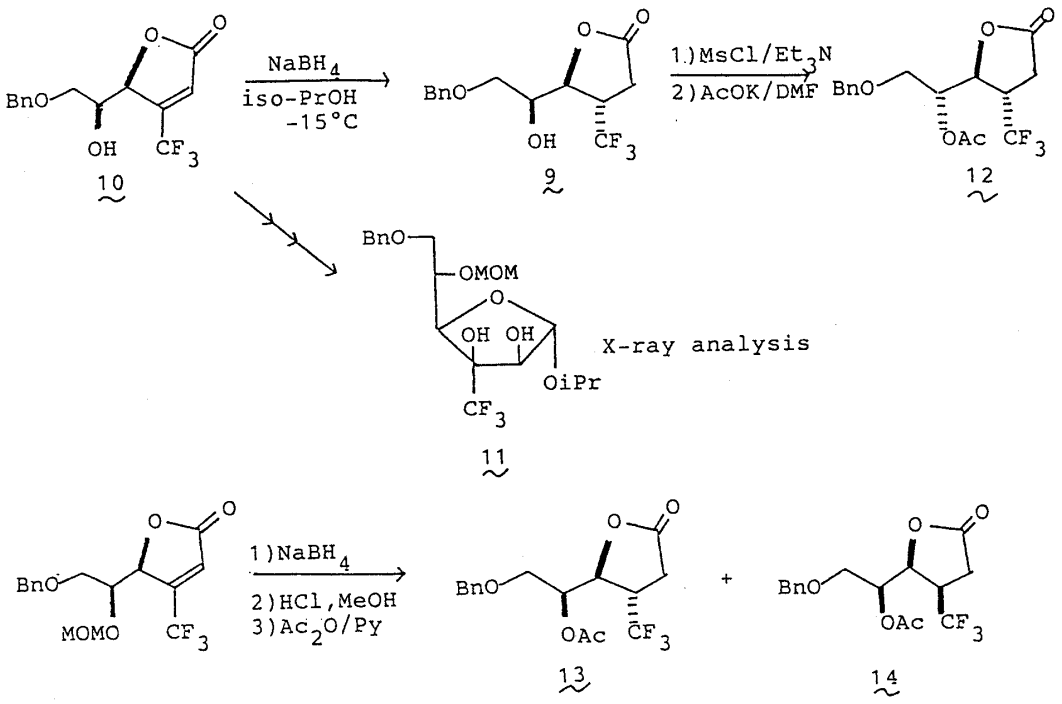


analysis.[5] Inversion of the hydroxyl group in 9 ($MsCl/Et_3N/CH_2Cl_2$, AcOK/DMF, 110°C) gave an acetate identical with that of 8 (12),[6] as indicated by NMR spectra comparison. These findings clearly demonstrate the structure of 8 to be 3,4-trans, 4,5-erythro.

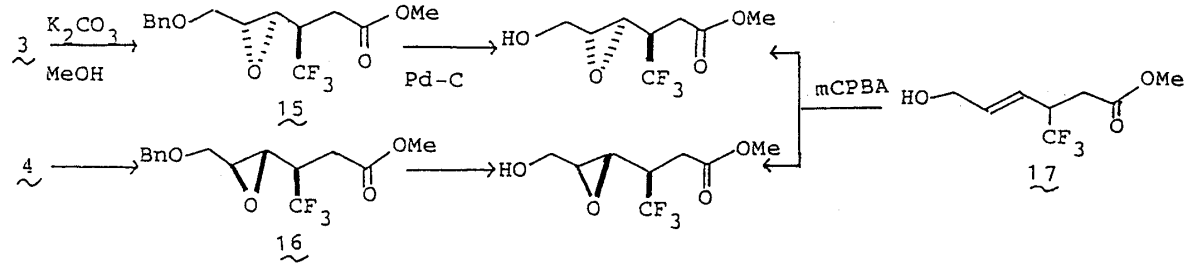
In the reduction of 10 with sodium borohydride, the hydroxyl group at $C_5$ was found to play a very important role. When the hydroxyl group was protected with methoxymethyl (MOM) group, a mixture of 3,4-trans (13) and 3,4-cis lactone (14) (1.6:1) was obtained. This stereospecific reduction of the C-C double bond ($NaBH_4$, iso-PrOH, -15°C) proceeded in 67% yield. Complexation of sodium borohydride with the hydroxy group may thus be assumed to occur first, followed by delivery of hydride onto the double bond from the same site of the $C_4$-substituent, to give 3,4-trans lactone (9).[7]

These hydroxylactones are considered to be important fragments in the preparation of the trifluoromethylated analog of polyhydroxyl compound which possesses an important biological activity.

Other useful frangments, such as epoxy esters (15, 16), were also prepared selectively by treating 3 and 4 with potassium carbonate in methanol (95% and 96%, respectively). These epoxides were also obtained in a poor ratio (2:1)[3] by the epoxidation of the ester of 1 with m-chloroperoxybenzoic acid (mCPBA). The epoxidation of the allylic alcohol derivative (17) obtained by reaction of the ester of 1 with trimethylsilyl iodide) (TMS iodide) gave threo- and erythro-epoxides in a 10:1




ratio (mCPBA, 0°C, 75% yield). Each structure was confirmed by comparison with the debenzylated products of 15 and 16. The syntheses of the fluorinated analogs of the branched sugars and aminosugars are now being studied.

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3) The ratio was determined by the integration of the $^{19}$F-NMR signals. All new compounds were identified by their NMR IR and mass spectra.

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6) 8; $^{1}$H-NMR($CDCl_3$) δ 2.10(3H, S), 2.68(1H, d, J=5Hz), 2.75(1H, d, J=9Hz), 3.20-3.70 (1H, m), 3.68(2H, d, J-5Hz), 4.53(2H, S), 4.88(1H, dd, J=4.5 and 4.5Hz), 5.20(1H, dt, J=4.5 and 5Hz), 7.38(5H, S).

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